

ALPRAZOLAM XR- alprazolam tablet, extended release
Greenstone LLC

Alprazolam XR CIV
(alprazolam)
extended-release tablets

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

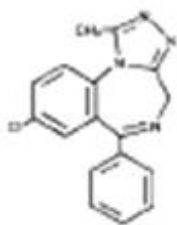
- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation (see WARNINGS and PRECAUTIONS).
- The use of benzodiazepines, including ALPRAZOLAM XR, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing ALPRAZOLAM XR and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (see WARNINGS).
- The continued use of benzodiazepines, including ALPRAZOLAM XR, may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and, higher daily dose. Abrupt discontinuation or rapid dosage reduction of ALPRAZOLAM XR after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue ALPRAZOLAM XR or reduce the dosage (see DOSAGE AND ADMINISTRATION and WARNINGS).

DESCRIPTION

Alprazolam XR tablets contain alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The chemical name of alprazolam is 8-chloro-1-methyl-6-phenyl-4*H*-s-triazolo [4,3- α] [1,4] benzodiazepine. The molecular formula is C₁₇H₁₃ClN₄ which corresponds to a molecular weight of 308.76.

The structural formula is represented below:



Alprazolam is a white crystalline powder, which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH.

Each Alprazolam XR extended-release tablet, for oral administration, contains 0.5 mg, 1 mg, 2 mg, or 3 mg of alprazolam. The inactive ingredients are lactose, magnesium stearate, colloidal silicon dioxide, and hypromellose. In addition, the 1 mg and 3 mg tablets contain D & C yellow No. 10 and the 2 mg and 3 mg tablets contain FD&C blue No. 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereospecific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Pharmacokinetics

Absorption

Following oral administration of Alprazolam (immediate-release) tablets, alprazolam is readily absorbed. Peak concentrations in the plasma occur in one to two hours following administration. Plasma levels are proportional to the dose given; over the dose range of 0.5 to 3.0 mg, peak levels of 8.0 to 37 ng/mL were observed. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 hours (range: 6.3–26.9 hours) in healthy adults.

The mean absolute bioavailability of alprazolam from Alprazolam XR tablets is approximately 90%, and the relative bioavailability compared to Alprazolam tablets is 100%. The bioavailability and pharmacokinetics of alprazolam following administration of Alprazolam XR tablets are similar to that for Alprazolam tablets, with the exception of a slower rate of absorption. The slower absorption rate results in a relatively constant concentration that is maintained between 5 and 11 hours after the dosing. The pharmacokinetics of alprazolam and two of its major active metabolites (4-hydroxyalprazolam and α -hydroxyalprazolam) are linear, and concentrations are proportional up to the recommended maximum daily dose of 10 mg given once daily. Multiple dose studies indicate that the metabolism and elimination of alprazolam are similar for the immediate-release and the extended-release products.

Food has a significant influence on the bioavailability of Alprazolam XR tablets. A high-fat meal given up to 2 hours before dosing with Alprazolam XR tablets increased the mean

C_{max} by about 25%. The effect of this meal on T_{max} depended on the timing of the meal, with a reduction in T_{max} by about 1/3 for subjects eating immediately before dosing and an increase in T_{max} by about 1/3 for subjects eating 1 hour or more after dosing. The extent of exposure (AUC) and elimination half-life ($t_{1/2}$) were not affected by eating.

There were significant differences in absorption rate for the Alprazolam XR tablet, depending on the time of day administered, with the C_{max} increased by 30% and the T_{max} decreased by an hour following dosing at night, compared to morning dosing.

Distribution

The apparent volume of distribution of alprazolam is similar for Alprazolam XR and Alprazolam tablets. In vitro, alprazolam is bound (80%) to human serum protein. Serum albumin accounts for the majority of the binding.

Metabolism

Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolam and α -hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam. The pharmacokinetic parameters at steady-state for the two hydroxylated metabolites of alprazolam (4-hydroxyalprazolam and α -hydroxyalprazolam) were similar for Alprazolam and Alprazolam XR tablets, indicating that the metabolism of alprazolam is not affected by absorption rate. The plasma concentrations of 4-hydroxyalprazolam and α -hydroxyalprazolam relative to unchanged alprazolam concentration after both Alprazolam XR and Alprazolam tablets were always less than 10% and 4%, respectively. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxyalprazolam and α -hydroxyalprazolam. Such low concentrations and the lesser potencies of 4-hydroxyalprazolam and α -hydroxyalprazolam suggest that they are unlikely to contribute much to the pharmacological effects of alprazolam. The benzophenone metabolite is essentially inactive.

Elimination

Alprazolam and its metabolites are excreted primarily in the urine. The mean plasma elimination half-life of alprazolam following administration of Alprazolam XR tablet ranges from 10.7–15.8 hours in healthy adults.

Special Populations

While pharmacokinetic studies have not been performed in special populations with Alprazolam XR tablets, the factors (such as age, gender, hepatic or renal impairment) that would affect the pharmacokinetics of alprazolam after the administration of Alprazolam tablets would not be expected to be different with the administration of Alprazolam XR tablets.

Changes in the absorption, distribution, metabolism, and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function, and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 hours has been observed in healthy elderly subjects (range: 9.0–26.9 hours, $n=16$) compared to 11.0 hours (range: 6.3–

15.8 hours, n=16) in healthy adult subjects. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5.8 and 65.3 hours (mean: 19.7 hours, n=17) as compared to between 6.3 and 26.9 hours (mean=11.4 hours, n=17) in healthy subjects. In an obese group of subjects the half-life of alprazolam ranged between 9.9 and 40.4 hours (mean=21.8 hours, n=12) as compared to between 6.3 and 15.8 hours (mean=10.6 hours, n=12) in healthy subjects.

Because of its similarity to other benzodiazepines, it is assumed that alprazolam undergoes transplacental passage and that it is excreted in human milk.

Race

Maximal concentrations and half-life of alprazolam are approximately 15% and 25% higher in Asians compared to Caucasians.

Pediatrics

The pharmacokinetics of alprazolam after administration of the Alprazolam XR tablet in pediatric patients have not been studied.

Gender

Gender has no effect on the pharmacokinetics of alprazolam.

Cigarette Smoking

Alprazolam concentrations may be reduced by up to 50% in smokers compared to non-smokers.

Drug-Drug Interactions

Alprazolam is primarily eliminated by metabolism via cytochrome P450 3A (CYP3A). Most of the interactions that have been documented with alprazolam are with drugs that inhibit or induce CYP3A4.

Compounds that are potent inhibitors of CYP3A would be expected to increase plasma alprazolam concentrations. Drug products that have been studied in vivo, along with their effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98 fold; itraconazole, 2.70 fold; nefazodone, 1.98 fold; fluvoxamine, 1.96 fold; and erythromycin, 1.61 fold (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS – Drug Interactions).

CYP3A inducers would be expected to decrease alprazolam concentrations and this has been observed in vivo. The oral clearance of alprazolam (given in a 0.8 mg single dose) was increased from 0.90 ± 0.21 mL/min/kg to 2.13 ± 0.54 mL/min/kg and the elimination $t_{1/2}$ was shortened (from 17.1 ± 4.9 to 7.7 ± 1.7 h) following administration of 300 mg/day carbamazepine for 10 days (see PRECAUTIONS – Drug Interactions). However, the carbamazepine dose used in this study was fairly low compared to the recommended doses (1000–1200 mg/day); the effect at usual carbamazepine doses is unknown.

The ability of alprazolam to induce or inhibit human hepatic enzyme systems has not been determined. However, this is not a property of benzodiazepines in general. Further, alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

CLINICAL EFFICACY TRIALS

The efficacy of Alprazolam XR tablets in the treatment of panic disorder was established in two 6-week, placebo-controlled studies of Alprazolam XR in patients with panic disorder.

In two 6-week, flexible-dose, placebo-controlled studies in patients meeting DSM-III criteria for panic disorder, patients were treated with Alprazolam XR in a dose range of 1 to 10 mg/day, on a once-a-day basis. The effectiveness of Alprazolam XR was assessed on the basis of changes in various measures of panic attack frequency, on various measures of the Clinical Global Impression, and on the Overall Phobia Scale. In all, there were seven primary efficacy measures in these studies, and Alprazolam XR was superior to placebo on all seven outcomes in both studies. The mean dose of Alprazolam XR at the last treatment visit was 4.2 mg/day in the first study and 4.6 mg/day in the second.

In addition, there were two 8-week, fixed-dose, placebo-controlled studies of Alprazolam XR in patients with panic disorder, involving fixed Alprazolam XR doses of 4 and 6 mg/day, on a once-a-day basis, that did not show a benefit for either dose of Alprazolam XR.

The longer-term efficacy of Alprazolam XR in panic disorder has not been systematically evaluated.

Analyses of the relationship between treatment outcome and gender did not suggest any differential responsiveness on the basis of gender.

INDICATIONS AND USAGE

Alprazolam XR tablets are indicated for the treatment of panic disorder, with or without agoraphobia.

This claim is supported on the basis of two positive studies with Alprazolam XR conducted in patients whose diagnoses corresponded closely to the DSM-III-R/IV criteria for panic disorder (see CLINICAL EFFICACY TRIALS).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, ie, a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The longer-term efficacy of Alprazolam XR has not been systematically evaluated. Thus, the physician who elects to use this drug for periods longer than 8 weeks should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Alprazolam XR tablets are contraindicated in patients with known sensitivity to this drug

or other benzodiazepines.

Alprazolam XR is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A) (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS – Drug Interactions).

WARNINGS

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including Alprazolam XR, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe Alprazolam XR concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of Alprazolam XR than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking Alprazolam XR, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Alprazolam XR is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined (see PRECAUTIONS – Drug Interactions).

Abuse, Misuse, and Addiction

The use of benzodiazepines, including Alprazolam XR, exposes users to the risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death (see DRUG ABUSE AND DEPENDENCE – Abuse).

Before prescribing Alprazolam XR and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (e.g., using a standardized screening tool). Use of Alprazolam XR, particularly in patients at elevated risk, necessitates counseling about the risks and proper use of Alprazolam XR along with monitoring for signs and symptoms of abuse, misuse, and addiction. Prescribe the lowest effective dosage; avoid or minimize concomitant use of CNS depressants and other substances associated with abuse, misuse, and addiction (e.g., opioid analgesics, stimulants); and advise patients on the proper disposal of unused drug. If a substance use disorder is suspected, evaluate the patient and institute (or refer them for) early treatment, as appropriate.

Dependence and Withdrawal Reactions

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue Alprazolam XR or reduce the dosage (a patient-specific plan should be used to taper the dose) (see DOSAGE AND ADMINISTRATION – Discontinuation or Dosage Reduction of Alprazolam XR).

Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages, and those who have had longer durations of use.

Acute Withdrawal Reactions

The continued use of benzodiazepines, including Alprazolam XR, may lead to clinically significant physical dependence. Abrupt discontinuation or rapid dosage reduction of Alprazolam XR after continued use, or administration of flumazenil (a benzodiazepine antagonist) may precipitate acute withdrawal reactions, which can be life-threatening (e.g., seizures) (see DRUG ABUSE AND DEPENDENCE – Dependence).

Protracted Withdrawal Syndrome

In some cases, benzodiazepine users have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months (see DRUG ABUSE AND DEPENDENCE – Dependence).

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to alprazolam. These include a spectrum of withdrawal symptoms; the most important is seizure (see DRUG ABUSE AND DEPENDENCE). Even after relatively short-term use at doses of ≤ 4 mg/day, there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks). However, in a controlled postmarketing discontinuation study of panic disorder patients who received Alprazolam tablets, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of Alprazolam tablets greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline.

The rate of relapse, rebound, and withdrawal in patients with panic disorder who received Alprazolam XR tablets has not been systematically studied. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder who received Alprazolam tablets showed a high rate of rebound and withdrawal symptoms compared to placebo treated patients.

In a controlled clinical trial in which 63 patients were randomized to Alprazolam tablets and where withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration,

dysosmia, clouded sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease, and weight loss. Other symptoms, such as anxiety and insomnia, were frequently seen during discontinuation, but it could not be determined if they were due to return of illness, rebound, or withdrawal.

In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue medication was measured, 71%–93% of patients treated with Alprazolam tablets tapered completely off therapy compared to 89%–96% of placebo treated patients. In a controlled postmarketing discontinuation study of panic disorder patients treated with Alprazolam tablets, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose.

Seizures were reported for three patients in panic disorder clinical trials with Alprazolam XR. In two cases, the patients had completed 6 weeks of treatment with Alprazolam XR 6 mg/day before experiencing a single seizure. In one case, the patient abruptly discontinued Alprazolam XR, and in both cases, alcohol intake was implicated. The third case involved multiple seizures after the patient completed treatment with Alprazolam XR 4 mg/day and missed taking the medication on the first day of taper. All three patients recovered without sequelae.

Seizures have also been observed in association with dose reduction or discontinuation of Alprazolam tablets, the immediate release form of alprazolam. Seizures attributable to Alprazolam were seen after drug discontinuance or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of Alprazolam greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2 to 10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every three days from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4 to 22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from Alprazolam. The risk of seizure seems to be greatest 24–72 hours after discontinuation (see DOSAGE AND ADMINISTRATION – Discontinuation or Dosage Reduction of Alprazolam XR).

Status Epilepticus

The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of Alprazolam tablets. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well.

Interdose Symptoms

Early morning anxiety and emergence of anxiety symptoms between doses of Alprazolam tablets have been reported in patients with panic disorder taking prescribed maintenance doses. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound, or

withdrawal symptoms over the entire course of the interdosing interval.

CNS Depression and Impaired Performance

Because of its CNS depressant effects, patients receiving Alprazolam XR should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with Alprazolam XR.

Risk of Fetal Harm

Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, alprazolam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

Alprazolam Interaction With Drugs That Inhibit Metabolism Via Cytochrome P450 3A

The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A. With drugs inhibiting CYP3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from in vitro data and/or experience with similar drugs in the same pharmacologic class.

The following are examples of drugs known to inhibit the metabolism of alprazolam and/or related benzodiazepines, presumably through inhibition of CYP3A.

Potent CYP3A Inhibitors

Azole antifungal agents

Ketoconazole and itraconazole are potent CYP3A inhibitors and have been shown in vivo to increase plasma alprazolam concentrations 3.98 fold and 2.70 fold, respectively. The coadministration of alprazolam with these agents is not recommended. Other azole-type antifungal agents should also be considered potent CYP3A inhibitors and the coadministration of alprazolam with them is not recommended (see CONTRAINDICATIONS).

Drugs demonstrated to be CYP3A inhibitors on the basis of clinical studies involving alprazolam (caution and consideration of appropriate alprazolam dose reduction are

recommended during coadministration with the following drugs)

Nefazodone

Coadministration of nefazodone increased alprazolam concentration two-fold.

Fluvoxamine

Coadministration of fluvoxamine approximately doubled the maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance.

Cimetidine

Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.

Other Drugs Possibly Affecting Alprazolam Metabolism

Other drugs possibly affecting alprazolam metabolism by inhibition of CYP3A are discussed in the PRECAUTIONS section (see PRECAUTIONS – Drug Interactions).

PRECAUTIONS

General

Suicide

As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.

Mania

Episodes of hypomania and mania have been reported in association with the use of Alprazolam tablets in patients with depression.

Uricosuric Effect

Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric effect have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with alprazolam.

Use in Patients with Concomitant Illness

It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients (see DOSAGE AND ADMINISTRATION). The usual precautions in treating patients with impaired renal, hepatic, or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with Alprazolam tablets. A decreased

systemic alprazolam elimination rate (e.g., increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving Alprazolam tablets (see CLINICAL PHARMACOLOGY).

Information for Patients

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Risks from Concomitant Use with Opioids

Advise both patients and caregivers about the risks of potentially fatal respiratory depression and sedation when Alprazolam XR is used with opioids and not to use such drugs concomitantly unless supervised by a health care provider. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined (see PRECAUTIONS - Drug Interactions).

Abuse, Misuse, and Addiction

Inform patients that the use of Alprazolam XR, even at recommended dosages, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose and death, especially when used in combination with other medications (e.g., opioid analgesics), alcohol, and/or illicit substances. Inform patients about the signs and symptoms of benzodiazepine abuse, misuse, and addiction; to seek medical help if they develop these signs and/or symptoms; and on the proper disposal of unused drug (see WARNINGS - Abuse, Misuse, and Addiction and DRUG ABUSE AND DEPENDENCE).

Withdrawal Reactions

Inform patients that the continued use of Alprazolam XR may lead to clinically significant physical dependence and that abrupt discontinuation or rapid dosage reduction of Alprazolam XR may precipitate acute withdrawal reactions, which can be life-threatening. Inform patients that in some cases, patients taking benzodiazepines have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months. Instruct patients that discontinuation or dosage reduction of Alprazolam XR may require a slow taper (see WARNINGS - Dependence and Withdrawal Reactions and DRUG ABUSE AND DEPENDENCE).

Inform your physician about any alcohol consumption and medicine you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.

Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.

Inform your physician if you are nursing.

Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.

Laboratory Tests

Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry

analyses are advisable in keeping with good medical practice.

Drug Interactions

Use with Opioids

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABA_A sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and monitor patients closely for respiratory depression and sedation.

Use with Other CNS Depressants

If Alprazolam XR tablets are to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed, particularly with compounds which might potentiate the action of benzodiazepines. The benzodiazepines, including alprazolam, produce additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

Use with Imipramine and Desipramine

The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20%, respectively, by the concomitant administration of Alprazolam tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.

Drugs that inhibit alprazolam metabolism via cytochrome P450 3A

The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs of this type).

Drugs demonstrated to be CYP3A inhibitors of possible clinical significance on the basis of clinical studies involving alprazolam (caution is recommended during coadministration with alprazolam)

Fluoxetine

Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance.

Propoxyphene

Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%.

Oral Contraceptives

Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

Drugs and other substances demonstrated to be CYP3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to alprazolam or on the basis of in vitro studies with alprazolam or other benzodiazepines (caution is recommended during coadministration with alprazolam)

Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from in vitro studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. However, data from an in vivo drug interaction study involving a single dose of alprazolam 1 mg and steady state doses of sertraline (50 to 150 mg/day) did not reveal any clinically significant changes in the pharmacokinetics of alprazolam. Data from in vitro studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the coadministration of any of these with alprazolam (see WARNINGS).

Drugs demonstrated to be inducers of CYP3A

Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam.

Drug/Laboratory Test Interactions

Although interactions between benzodiazepines and commonly employed clinical laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day.

Alprazolam also was not mutagenic in vitro in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

Pregnancy

Teratogenic Effects

Pregnancy Category D

(see WARNINGS section).

Nonteratogenic Effects

It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.

Labor and Delivery

Alprazolam has no established use in labor or delivery.

Nursing Mothers

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use alprazolam.

Pediatric Use

Safety and effectiveness of alprazolam in individuals below 18 years of age have not been established.

Geriatric Use

The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The smallest effective dose of alprazolam should be used in the elderly to preclude the development of ataxia and oversedation (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The information included in the subsection on Adverse Events Observed in Short-Term, Placebo-Controlled Trials with Alprazolam XR tablets is based on pooled data of five 6- and 8-week placebo-controlled clinical studies in panic disorder.

Adverse event reports were elicited either by general inquiry or by checklist, and were recorded by clinical investigators using terminology of their own choosing. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened during therapy following baseline evaluation. In the tables and tabulations that follow, standard MedDRA terminology (version 4.0) was used to classify reported adverse events.

Adverse Events Observed in Short-Term, Placebo-Controlled Trials of Alprazolam XR

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials

Approximately 17% of the 531 patients who received Alprazolam XR in placebo-controlled clinical trials for panic disorder had at least one adverse event that led to discontinuation compared to 8% of 349 placebo-treated patients. The most common events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of the patients treated with Alprazolam XR at a rate at least twice that of placebo) are shown in the following table.

Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials

System Organ Class/Adverse Event	Percentage of Patients Discontinuing Due to Adverse Events	
	Alprazolam XR (n=531)	Placebo (n=349)
Nervous system disorders		
Sedation	7.5	0.6
Somnolence	3.2	0.3
Dysarthria	2.1	0
Coordination abnormal	1.9	0.3
Memory impairment	1.5	0.3
General disorders/administration site conditions		
Fatigue	1.7	0.6
Psychiatric disorders		
Depression	2.5	1.2

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated with Alprazolam XR

The prescriber should be aware that adverse event incidence cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with event incidence obtained from other clinical investigations involving different treatments, uses, and investigators. The cited values, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The following table shows the incidence of treatment-emergent adverse events that occurred during 6 to 8-week placebo-controlled trials in 1% or more of patients treated with Alprazolam XR where the incidence in patients treated with Alprazolam XR was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in panic disorder patients treated with Alprazolam XR (incidence of 5% or greater and at least twice the incidence in placebo patients) were: sedation, somnolence, memory impairment, dysarthria, coordination abnormal, ataxia, libido decreased (see table).

**Treatment-Emergent Adverse Events: Incidence in
Short-Term, Placebo-Controlled Clinical Trials with
Alprazolam XR**

System Organ Class/Adverse Event	Percentage of Patients Reporting Adverse Event	
	Alprazolam XR (n=531)	Placebo (n=349)
Nervous system disorders		
Sedation	45.2	22.6
Somnolence	23.0	6.0
Memory impairment	15.4	6.9
Dysarthria	10.9	2.6
Coordination abnormal	9.4	0.9
Mental impairment	7.2	5.7
Ataxia	7.2	3.2
Disturbance in attention	3.2	0.6
Balance impaired	3.2	0.6
Paresthesia	2.4	1.7
Dyskinesia	1.7	1.4
Hypoesthesia	1.3	0.3
Hypersomnia	1.3	0
General disorders/administration site conditions		
Fatigue	13.9	9.2
Lethargy	1.7	0.6
Infections and infestations		
Influenza	2.4	2.3
Upper respiratory tract infections	1.9	1.7
Psychiatric disorders		
Depression	12.1	9.2
Libido decreased	6.0	2.3
Disorientation	1.5	0
Confusion	1.5	0.9
Depressed mood	1.3	0.3
Anxiety	1.1	0.6
Metabolism and nutrition disorders		
Appetite decreased	7.3	7.2
Appetite increased	7.0	6.0
Anorexia	1.5	0
Gastrointestinal		

disorders		
Dry mouth	10.2	9.7
Constipation	8.1	4.3
Nausea	6.0	3.2
Pharyngolaryngeal pain	3.2	2.6
Investigations		
Weight increased	5.1	4.3
Weight decreased	4.3	3.7
Injury, poisoning, and procedural complications		
Road traffic accident	1.5	0
Reproductive system and breast disorders		
Dysmenorrhea	3.6	2.9
Sexual dysfunction	2.4	1.1
Premenstrual syndrome	1.7	0.6
Musculoskeletal and connective tissue disorders		
Arthralgia	2.4	0.6
Myalgia	1.5	1.1
Pain in limb	1.1	0.3
Vascular disorders		
Hot flushes	1.5	1.4
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	1.5	0.3
Rhinitis allergic	1.1	0.6
Skin and subcutaneous tissue disorders		
Pruritis	1.1	0.9

Other Adverse Events Observed During the Premarketing Evaluation of Alprazolam XR tablets

Following is a list of MedDRA terms that reflect treatment-emergent adverse events reported by 531 patients with panic disorder treated with Alprazolam XR. All potentially important reported events are included except those already listed in the above table or elsewhere in labeling, those events for which a drug cause was remote, those event terms that were so general as to be uninformative, and those events that occurred at rates similar to background rates in the general population. It is important to emphasize that, although the events reported occurred during treatment with Alprazolam XR, they were not necessarily caused by the drug. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100

patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Cardiac disorders: *Frequent:* palpitation; *Infrequent:* sinus tachycardia

Ear and Labyrinth disorders: *Frequent:* Vertigo; *Infrequent:* tinnitus, ear pain

Eye disorders: *Frequent:* blurred vision; *Infrequent:* mydriasis, photophobia

Gastrointestinal disorders: *Frequent:* diarrhea, vomiting, dyspepsia, abdominal pain; *Infrequent:* dysphagia, salivary hypersecretion

General disorders and administration site conditions: *Frequent:* malaise, weakness, chest pains; *Infrequent:* fall, pyrexia, thirst, feeling hot and cold, edema, feeling jittery, sluggishness, asthenia, feeling drunk, chest tightness, increased energy, feeling of relaxation, hangover, loss of control of legs, rigors

Musculoskeletal and connective tissue disorders: *Frequent:* back pain, muscle cramps, muscle twitching

Nervous system disorders: *Frequent:* headache, dizziness, tremor; *Infrequent:* amnesia, clumsiness, syncope, hypotonia, seizures, depressed level of consciousness, sleep apnea syndrome, sleep talking, stupor

Psychiatric system disorders: *Frequent:* irritability, insomnia, nervousness, derealization, libido increased, restlessness, agitation, depersonalization, nightmare; *Infrequent:* abnormal dreams, apathy, aggression, anger, bradyphrenia, euphoric mood, logorrhea, mood swings, dysphonia, hallucination, homicidal ideation, mania, hypomania, impulse control, psychomotor retardation, suicidal ideation

Renal and urinary disorders: *Frequent:* difficulty in micturition; *Infrequent:* urinary frequency, urinary incontinence

Respiratory, thoracic, and mediastinal disorders: *Frequent:* nasal congestion, hyperventilation; *Infrequent:* choking sensation, epistaxis, rhinorrhea

Skin and subcutaneous tissue disorders: *Frequent:* sweating increased; *Infrequent:* clamminess, rash, urticaria

Vascular disorders: *Infrequent:* hypotension

The categories of adverse events reported in the clinical development program for Alprazolam tablets in the treatment of panic disorder differ somewhat from those reported for Alprazolam XR tablets because the clinical trials with Alprazolam tablets and Alprazolam XR tablets used different standard medical nomenclature for reporting the adverse events. Nevertheless, the types of adverse events reported in the clinical trials with Alprazolam tablets were generally the same as those reported in the clinical trials with Alprazolam XR tablets.

Discontinuation-Emergent Adverse Events Occurring at an Incidence of 5% or More Among Patients Treated with Alprazolam XR

The following table shows the incidence of discontinuation-emergent adverse events that occurred during short-term, placebo-controlled trials in 5% or more of patients treated with Alprazolam XR where the incidence in patients treated with Alprazolam XR was two times greater than the incidence in placebo-treated patients.

Discontinuation-Emergent Symptoms: Incidence in Short-Term, Placebo-Controlled Trials with Alprazolam XR

System Organ Class/Adverse Event	Percentage of Patients Reporting Adverse Event	
	Alprazolam XR (n=422)	Placebo (n=261)
Nervous system disorders		
Tremor	28.2	10.7
Headache	26.5	12.6
Hypoesthesia	7.8	2.3
Paraesthesia	7.1	2.7
Psychiatric disorders		
Insomnia	24.2	9.6
Nervousness	21.8	8.8
Depression	10.9	5.0
Derealization	8.0	3.8
Anxiety	7.8	2.7
Depersonalization	5.7	1.9
Gastrointestinal disorders		
Diarrhea	12.1	3.1
Respiratory, thoracic and mediastinal disorders		
Hyperventilation	8.5	2.7
Metabolism and nutrition disorders		
Appetite decreased	9.5	3.8
Musculoskeletal and connective tissue disorders		
Muscle twitching	7.4	2.7
Vascular disorders		
Hot flushes	5.9	2.7

There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam (see WARNINGS).

To discontinue treatment in patients taking Alprazolam XR tablets, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of Alprazolam XR tablets be decreased by no more than 0.5 mg every three days (see DOSAGE AND ADMINISTRATION). Some patients may benefit from an even slower dosage reduction. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients

who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations, and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients who have borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

Post Introduction Reports

Various adverse drug reactions have been reported in association with the use of Alprazolam tablets since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of Alprazolam tablets cannot be readily determined. Reported events include: gastrointestinal disorder, hypomania, mania, liver enzyme elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, angioedema, peripheral edema, hyperprolactinemia, gynecomastia, and galactorrhea (see PRECAUTIONS).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Alprazolam XR contains alprazolam, a Schedule IV controlled substance.

Abuse

Alprazolam XR is a benzodiazepine and a CNS depressant with a potential for abuse and addiction. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence. Even taking benzodiazepines as prescribed may put patients at risk for abuse and misuse of their medication. Abuse and misuse of benzodiazepines may lead to addiction.

Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death. Benzodiazepines are often sought by individuals who abuse drugs

and other substances, and by individuals with addictive disorders (see WARNINGS – Abuse, Misuse, and Addiction).

The following adverse reactions have occurred with benzodiazepine abuse and/or misuse: abdominal pain, amnesia, anorexia, anxiety, aggression, ataxia, blurred vision, confusion, depression, disinhibition, disorientation, dizziness, euphoria, impaired concentration and memory, indigestion, irritability, muscle pain, slurred speech, tremors, and vertigo.

The following severe adverse reactions have occurred with benzodiazepine abuse and/or misuse: delirium, paranoia, suicidal ideation and behavior, seizures, coma, breathing difficulty, and death. Death is more often associated with polysubstance use (especially benzodiazepines with other CNS depressants such as opioids and alcohol).

Dependence

Physical Dependence

Alprazolam XR may produce physical dependence from continued therapy. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Abrupt discontinuation or rapid dosage reduction of benzodiazepines or administration of flumazenil, a benzodiazepine antagonist, may precipitate acute withdrawal reactions, including seizures, which can be life-threatening. Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages (i.e., higher and/or more frequent doses) and those who have had longer durations of use (see WARNINGS - Dependence and Withdrawal Reactions).

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue Alprazolam XR or reduce the dosage (see DOSAGE AND ADMINISTRATION – Discontinuation or Dosage Reduction of Alprazolam XR and WARNINGS – Dependence and Withdrawal Reactions).

Acute Withdrawal Signs and Symptoms

Acute withdrawal signs and symptoms associated with benzodiazepines have included abnormal involuntary movements, anxiety, blurred vision, depersonalization, depression, derealization, dizziness, fatigue, gastrointestinal adverse reactions (e.g., nausea, vomiting, diarrhea, weight loss, decreased appetite), headache, hyperacusis, hypertension, irritability, insomnia, memory impairment, muscle pain and stiffness, panic attacks, photophobia, restlessness, tachycardia, and tremor. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included catatonia, convulsions, delirium tremens, depression, hallucinations, mania, psychosis, seizures and suicidality.

Protracted Withdrawal Syndrome

Protracted withdrawal syndrome associated with benzodiazepines is characterized by anxiety, cognitive impairment, depression, insomnia, formication, motor symptoms (e.g., weakness, tremor, muscle twitches), paresthesia, and tinnitus that persists beyond 4 to 6 weeks after initial benzodiazepine withdrawal. Protracted withdrawal symptoms may last weeks to more than 12 months. As a result, there may be difficulty in differentiating

withdrawal symptoms from potential re-emergence or continuation of symptoms for which the benzodiazepine was being used.

Tolerance

Tolerance to Alprazolam XR may develop from continued therapy. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to the therapeutic effect of Alprazolam XR may develop; however, little tolerance develops to the amnestic reactions and other cognitive impairments caused by benzodiazepines.

OVERDOSAGE

Clinical Experience

Overdosage reports with Alprazolam tablets are limited. Manifestations of alprazolam overdosage include somnolence, confusion, impaired coordination, diminished reflexes, and coma. Death has been reported in association with overdoses of alprazolam by itself, as it has with other benzodiazepines. In addition, fatalities have been reported in patients who have overdosed with a combination of a single benzodiazepine, including alprazolam, and alcohol; alcohol levels seen in some of these patients have been lower than those usually associated with alcohol-induced fatality.

Animal experiments have suggested that forced diuresis or hemodialysis are probably of little value in treating overdosage.

General Treatment of Overdose

As in all cases of drug overdosage, respiration, pulse rate, and blood pressure should be monitored. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. If hypotension occurs, it may be combated by the use of vasopressors. Dialysis is of limited value. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.

Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation, and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS should be consulted prior to use.

DOSAGE AND ADMINISTRATION

Alprazolam XR tablets may be administered once daily, preferably in the morning. The tablets should be taken intact; they should not be chewed, crushed, or broken.

The suggested total daily dose ranges between 3 to 6 mg/day. Dosage should be individualized for maximum beneficial effect. While the suggested total daily dosages given will meet the needs of most patients, there will be some patients who require doses greater than 6 mg/day. In such cases, dosage should be increased cautiously to avoid adverse effects.

Dosing in Special Populations

In elderly patients, in patients with advanced liver disease, or in patients with debilitating disease, the usual starting dose of Alprazolam XR is 0.5 mg once daily. This may be gradually increased if needed and tolerated (see Dose Titration). The elderly may be especially sensitive to the effects of benzodiazepines.

Dose Titration

Treatment with Alprazolam XR may be initiated with a dose of 0.5 mg to 1 mg once daily. Depending on the response, the dose may be increased at intervals of 3 to 4 days in increments of no more than 1 mg/day. Slower titration to the dose levels may be advisable to allow full expression of the pharmacodynamic effect of Alprazolam XR.

Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Dose should be advanced until an acceptable therapeutic response (i.e., a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained.

Dose Maintenance

In controlled trials conducted to establish the efficacy of Alprazolam XR tablets in panic disorder, doses in the range of 1 to 10 mg/day were used. Most patients showed efficacy in the dose range of 3 to 6 mg/day. Occasional patients required as much as 10 mg/day to achieve a successful response.

The necessary duration of treatment for panic disorder patients responding to Alprazolam XR is unknown. However, periodic reassessment is advised. After a period of extended freedom from attacks, a carefully supervised tapered discontinuation may be attempted, but there is evidence that this may often be difficult to accomplish without recurrence of symptoms and/or the manifestation of withdrawal phenomena.

Discontinuation or Dosage Reduction of Alprazolam XR

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue Alprazolam XR or reduce the dosage. If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level. Subsequently decrease the dosage more slowly (see WARNINGS – Dependence and Withdrawal Reactions and DRUG ABUSE AND DEPENDENCE – Dependence).

In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero

dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

Reduce the dosage by no more than 0.5 mg every three days. Some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

Switch from alprazolam (immediate-release) tablets to Alprazolam XR (extended-release) tablets

Patients who are currently being treated with divided doses of alprazolam (immediate-release) tablets, for example 3 to 4 times a day, may be switched to Alprazolam XR tablets at the same total daily dose taken once daily. If the therapeutic response after switching is inadequate, the dosage may be titrated as outlined above.

HOW SUPPLIED

Alprazolam XR (extended-release) tablets are available as follows:

0.5 mg (white, pentagonal-shaped tablets debossed with an "G" on one side and "0.5" on the other side)

Bottles of 60	NDC 59762-0057-1
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1 mg (yellow, square-shaped tablets debossed with an "G" on one side and "1" on the other side)

Bottles of 60	NDC 59762-0059-1
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2 mg (blue, round-shaped tablets debossed with an "G" on one side and "2" on the other side)

Bottles of 60	NDC 59762-0066-1
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3 mg (green, triangular-shaped tablets debossed with an "G" on one side and "3" on the other side)

Bottles of 60	NDC 59762-0068-1
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Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

ANIMAL STUDIES

When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended human dose) orally for 2 years, a tendency for a dose related increase in the number of cataracts was observed in females and a tendency for a dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

This product's labeling may have been updated. For the most recent prescribing information, please visit www.greenstonellc.com.



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MEDICATION GUIDE ALPRAZOLAM XR Tablets, C-IV

What is the most important information I should know about Alprazolam XR?

- **Alprazolam XR is a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system (CNS) depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma and death. Get emergency help right away if any of the following happens:**
 - shallow or slowed breathing
 - breathing stops (which may lead to the heart stopping)
 - excessive sleepiness (sedation)Do not drive or operate heavy machinery until you know how taking Alprazolam XR with opioids affects you.
- **Risk of abuse, misuse, and addiction.** There is a risk of abuse, misuse, and addiction with benzodiazepines including Alprazolam XR which can lead to overdose and serious side effects including coma and death.
 - **Serious side effects including coma and death have happened in people who have abused or misused benzodiazepines, including Alprazolam XR.** These serious side effects may also include delirium, paranoia, suicidal thoughts or actions, seizures, and difficulty breathing. **Call your healthcare provider or go to the nearest hospital emergency room right away if you get any of these serious side effects.**
 - **You can develop an addiction even if you take Alprazolam XR as prescribed by your healthcare provider.**
 - **Take Alprazolam XR exactly as your healthcare provider prescribed.**
 - Do not share your Alprazolam XR with other people.
 - Keep Alprazolam XR in a safe place and away from children.
- **Physical dependence and withdrawal reactions.** Alprazolam XR can cause

physical dependence and withdrawal reactions.

- **Do not suddenly stop taking Alprazolam XR.** Stopping Alprazolam XR suddenly can cause serious and life-threatening side effects, including, unusual movements, responses, or expressions, seizures, sudden and severe mental or nervous system changes, depression, seeing or hearing things that others do not see or hear, an extreme increase in activity or talking, losing touch with reality, and suicidal thoughts or actions. **Call your healthcare provider or go to the nearest hospital emergency room right away if you get any of the following symptoms.**
- **Some people who suddenly stop benzodiazepines, have symptoms that can last for several weeks to more than 12 months,** including, anxiety, trouble remembering, learning, or concentrating, depression, problems sleeping, feeling like insects are crawling under your skin, weakness, shaking, muscle twitching, burning or prickling feeling in your hands, arms, legs or feet, and ringing in your ears.
- Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.
- Do not take more Alprazolam XR than prescribed or take Alprazolam XR for longer than prescribed.

What is Alprazolam XR?

- Alprazolam XR is a prescription medicine used to treat panic disorder, with or without a fear of places and situations that might cause panic, helplessness, or embarrassment (agoraphobia)
- **Alprazolam XR is a federal controlled substance (C-IV) because it contains alprazolam that can be abused or lead to dependence.** Keep Alprazolam XR in a safe place to prevent misuse and abuse. Selling or giving away Alprazolam XR may harm others and is against the law. Tell your healthcare provider if you have abused or been dependent on alcohol, prescription medicines or street drugs.
- It is not known if Alprazolam XR is safe and effective in children.
- Elderly patients are especially susceptible to dose related adverse effects when taking Alprazolam XR.
- It is not known if Alprazolam XR is safe and effective in the treatment of panic disorder for use longer than 8 weeks.

Do not take Alprazolam XR if:

- you are allergic to alprazolam, other benzodiazepines, or any of the ingredients in Alprazolam XR. See the end of this Medication Guide for a complete list of ingredients in Alprazolam XR.
- you are taking antifungal medicines including ketoconazole and itraconazole

Before you take Alprazolam XR, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had depression, mood problems, or suicidal thoughts or behavior
- have liver or kidney problems
- have lung disease or breathing problems
- are pregnant or plan to become pregnant. Alprazolam XR may harm your unborn baby. You and your healthcare provider should decide if you should take Alprazolam

XR while you are pregnant.

- are breastfeeding or plan to breastfeed. Alprazolam XR passes into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take Alprazolam XR. You should not breastfeed while taking Alprazolam XR.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking Alprazolam XR with certain other medicines can cause side effects or affect how well Alprazolam XR or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

How should I take Alprazolam XR?

- **See "What is the most important information I should know about Alprazolam XR?"**
- Take Alprazolam XR exactly as your healthcare provider tells you to take it. Your healthcare provider will tell you how much Alprazolam XR to take and when to take it.
- If you take too much Alprazolam XR, call your healthcare provider or go to the nearest hospital emergency room right away.
- Swallow Alprazolam XR tablets whole. Do not crush, chew or break Alprazolam XR

What are the possible side effects of Alprazolam XR?

Alprazolam XR may cause serious side effects, including:

- **See "What is the most important information I should know about Alprazolam XR?"**
- **Seizures.** Stopping Alprazolam XR can cause seizures and seizures that will not stop (status epilepticus).
- **Mania.** Alprazolam XR may cause an increase in activity and talking (hypomania and mania) in people who have depression.
- **Alprazolam XR can make you sleepy or dizzy and can slow your thinking and motor skills.**
 - Do not drive, operate heavy machinery, or do other dangerous activities until you know how Alprazolam XR affects you.
 - **Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking Alprazolam XR without first talking to your healthcare provider.** When taken with alcohol or drugs that cause sleepiness or dizziness, Alprazolam XR may make your sleepiness or dizziness much worse.

The most common side effects of Alprazolam XR include:

- | | |
|--------------------------------|-------------------|
| • sedation | • drowsiness |
| • trouble saying words clearly | • depression |
| • problems with coordination | • memory problems |
| • tiredness | |

These are not all the possible side effects of Alprazolam XR. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Alprazolam XR?

- Store Alprazolam XR at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep Alprazolam XR and all medicines out of the reach of children.**

- **General information about the safe and effective use of Alprazolam XR.**
- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- Do not use Alprazolam XR for a condition for which it was not prescribed.
- Do not give Alprazolam XR to other people, even if they have the same symptoms that you have. It may harm them.
- You can ask your pharmacist or healthcare provider for information about Alprazolam XR that is written for health professionals.

What are the ingredients in Alprazolam XR?

Active ingredient: alprazolam

Inactive ingredients: lactose, magnesium stearate, colloidal silicon dioxide, and hypromellose. In addition, the 1 mg and 3 mg tablets contain D & C yellow No. 10 and the 2 mg and 3 mg tablets contain FD&C blue No. 2.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: February 2021

This product's labeling may have been updated. For the most recent prescribing information, please visit www.greenstonellc.com.



GREENSTONE® BRAND

Distributed by:

Greenstone LLC
Peapack, NJ 07977

LAB-0823-2.0

PRINCIPAL DISPLAY PANEL - 0.5 mg Tablet Bottle Label

***ALWAYS DISPENSE WITH
MEDICATION GUIDE***

NDC 59762-0057-1

60 Tablets

GREENSTONE® BRAND

alprazolam XR

alprazolam

extended-release tablets

CIV

0.5 mg


Rx only

Store at 25°C (77°F);
excursions permitted to
15-30°C (59-86°F) [see USP
Controlled Room Temperature].

Dispense in tight (USP),
child-resistant containers.

DOSAGE AND USE

See accompanying
prescribing information.
Each tablet contains
0.5 mg alprazolam.

 Distributed by:
Greenstone LLC
Peapack, NJ 07977



423188903

**ALWAYS DISPENSE WITH
MEDICATION GUIDE**
NDC 59762-0057-1
60 Tablets

GREENSTONE® BRAND

alprazolam XR
alprazolam
extended-release tablets

0.5 mg
R_x only

C
IV

GTIN:
00359762005717



N 3 59762-0057 -1 7

LOT/EXP

PRINCIPAL DISPLAY PANEL - 1 mg Tablet Bottle Label

**ALWAYS DISPENSE WITH
MEDICATION GUIDE**

NDC 59762-0059-1

60 Tablets

GREENSTONE® BRAND

alprazolam XR
alprazolam
extended-release tablets

CIV

1 mg

R_x only

Store at 25°C (77°F);
excursions permitted to
15-30°C (59-86°F) [see USP
Controlled Room Temperature].

Dispense in tight (USP),
child-resistant containers.

DOSAGE AND USE

See accompanying
prescribing information.

Each tablet contains
1 mg alprazolam.



Distributed by:
Greenstone LLC
Peapack, NJ 07977



423189003

**ALWAYS DISPENSE WITH
MEDICATION GUIDE**

NDC 59762-0059-1

60 Tablets

GREENSTONE® BRAND

alprazolam XR

alprazolam

extended-release tablets

1 mg

Rx only



GTIN:
00359762005915



N 3 59762-0059 -1 5

LOT/EXP

PRINCIPAL DISPLAY PANEL - 2 mg Tablet Bottle Label

**ALWAYS DISPENSE WITH
MEDICATION GUIDE**

NDC 59762-0066-1

60 Tablets

GREENSTONE® BRAND

alprazolam XR

alprazolam

extended-release tablets

CIV

2 mg


Rx only

Store at 25°C (77°F);
excursions permitted to
15-30°C (59-86°F) [see USP
Controlled Room Temperature].

Dispense in tight (USP),
child-resistant containers.

DOSAGE AND USE

See accompanying
prescribing information.
Each tablet contains
2 mg alprazolam.

 Distributed by:
Greenstone LLC
Peapack, NJ 07977



423189103

**ALWAYS DISPENSE WITH
MEDICATION GUIDE**
NDC 59762-0066-1
60 Tablets

GREENSTONE® BRAND

alprazolam XR
alprazolam
extended-release tablets

2 mg

R_x only



GTIN:
00359762006615



LOT/EXP
N3 59762-0066 -1 5

PRINCIPAL DISPLAY PANEL - 3 mg Tablet Bottle Label

**ALWAYS DISPENSE WITH
MEDICATION GUIDE**

NDC 59762-0068-1

60 Tablets

GREENSTONE® BRAND

alprazolam XR

alprazolam


extended-release tablets

CIV

3 mg

R_x only

Store at 25°C (77°F);
excursions permitted to
15-30°C (59-86°F) [see USP
Controlled Room Temperature].
Dispense in tight (USP),
child-resistant containers.
DOSAGE AND USE
See accompanying
prescribing information.
Each tablet contains
3 mg alprazolam.

 Distributed by:
Greenstone LLC
Peapack, NJ 07977



423189203

**ALWAYS DISPENSE WITH
MEDICATION GUIDE**
NDC 59762-0068-1
60 Tablets

GREENSTONE® BRAND

alprazolam XR
alprazolam
extended-release tablets

3 mg
R_x only



GTIN:
00359762006813



N 3 59762-0068 -1 3

LOT/EXP

ALPRAZOLAM XR

alprazolam tablet, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:59762-0057
Route of Administration	ORAL	DEA Schedule	CIV

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ALPRAZOLAM (UNII: YU55MQ3IZY) (ALPRAZOLAM - UNII:YU55MQ3IZY)	ALPRAZOLAM	0.5 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	

Product Characteristics

Color	WHITE	Score	no score
Shape	PENTAGON (5 SIDED) (pentagon)	Size	9mm
Flavor		Imprint Code	G;0;5
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59762-0057-1	60 in 1 BOTTLE; Type 0: Not a Combination Product	01/17/2003	
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA AUTHORIZED GENERIC		NDA021434	01/17/2003	

ALPRAZOLAM XR				
alprazolam tablet, extended release				
Product Information				
Product Type		HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:59762-0059
Route of Administration		ORAL	DEA Schedule	CIV
Active Ingredient/Active Moiety				
Ingredient Name			Basis of Strength	Strength
ALPRAZOLAM (UNII: YU55MQ3IZY) (ALPRAZOLAM - UNII:YU55MQ3IZY)			ALPRAZOLAM	1 mg
Inactive Ingredients				
Ingredient Name				Strength
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)				
MAGNESIUM STEARATE (UNII: 70097M6I30)				
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)				
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)				
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)				
Product Characteristics				
Color	YELLOW	Score	no score	
Shape	SQUARE	Size	8mm	
Flavor		Imprint Code	G;1	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59762-	60 in 1 BOTTLE; Type 0: Not a Combination	01/17/2003	

0059-1	Product	01/17/2003	
Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA AUTHORIZED GENERIC	NDA021434	01/17/2003	

ALPRAZOLAM XR				
alprazolam tablet, extended release				
Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:59762-0066	
Route of Administration	ORAL	DEA Schedule	CIV	
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
ALPRAZOLAM (UNII: YU55MQ3IZY) (ALPRAZOLAM - UNII:YU55MQ3IZY)		ALPRAZOLAM	2 mg	
Inactive Ingredients				
Ingredient Name			Strength	
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)				
MAGNESIUM STEARATE (UNII: 70097M6I30)				
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)				
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)				
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)				
Product Characteristics				
Color	BLUE	Score	no score	
Shape	ROUND	Size	10mm	
Flavor		Imprint Code	G;2	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59762-0066-1	60 in 1 BOTTLE; Type 0: Not a Combination Product	01/17/2003	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA AUTHORIZED GENERIC	NDA021434	01/17/2003	

ALPRAZOLAM XR

alprazolam tablet, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:59762-0068
Route of Administration	ORAL	DEA Schedule	CIV

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ALPRAZOLAM (UNII: YU55MQ3IZY) (ALPRAZOLAM - UNII:YU55MQ3IZY)	ALPRAZOLAM	3 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

Product Characteristics

Color	GREEN	Score	no score
Shape	TRIANGLE	Size	10mm
Flavor		Imprint Code	G;3
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59762-0068-1	60 in 1 BOTTLE; Type 0: Not a Combination Product	01/17/2003	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
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NDA AUTHORIZED GENERIC	NDA021434	01/17/2003	
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Labeler - Greenstone LLC (825560733)

Establishment

Name	Address	ID/FEI	Business Operations
Pfizer Pharmaceuticals LLC		829084545	ANALYSIS(59762-0057, 59762-0059, 59762-0066, 59762-0068) , MANUFACTURE(59762-0057, 59762-0059, 59762-0066, 59762-0068)

Establishment

Name	Address	ID/FEI	Business Operations
Pharmacia & Upjohn Company LLC		618054084	API MANUFACTURE(59762-0057, 59762-0059, 59762-0066, 59762-0068)

Establishment

Name	Address	ID/FEI	Business Operations
Pfizer Pharmaceuticals LLC		829084552	PACK(59762-0057, 59762-0059, 59762-0066, 59762-0068)

Establishment

Name	Address	ID/FEI	Business Operations
Pfizer Italia S.r.l.		458521908	ANALYSIS(59762-0057, 59762-0059, 59762-0066, 59762-0068) , MANUFACTURE(59762-0057, 59762-0059, 59762-0066, 59762-0068) , PACK(59762-0057, 59762-0059, 59762-0066, 59762-0068)

Establishment

Name	Address	ID/FEI	Business Operations
Pfizer Ireland Pharmaceuticals		986019327	ANALYSIS(59762-0057, 59762-0059, 59762-0066, 59762-0068) , MANUFACTURE(59762-0057, 59762-0059, 59762-0066, 59762-0068)

Revised: 4/2021

Greenstone LLC